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DRUG DISCOVERY

Multidrug resistant *Staphylococcus aureus:* A global challenge

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ABSTRACT

Multidrug resistance is one of the serious problems faced by public health at the beginning of twenty first century. It is usually associated with significant morbidity, longer hospitalization, excess costs and mortality. Staphylococcus aureus is a common pathogen in hospital and community acquired disease that causes a wide range of infection such as skin and soft tissue infection to life threatening disease like respiratory tract infection, meningitis, endocarditis, bacteraemia, musculoskeletal infection and urinary tract infection. Approximately 90% of Staphylococcus strains are resistant to penicillin. In 1961 S. aureus developed resistance to Methicillin (MRSA), invalidating almost all antibiotics, including the most potent β-lactams. Quinolones, such as ciprofloxacin with increased anti-staphylococcal activity are available but their use may become limited due to the rapid development of resistance and allergic reaction during therapy. Vancomycin, a glycopeptides antibiotic, was used for the treatment of MRSA in 1980. Vancomycin resistant S. aureus (VRSA) first detected in the USA in 2002. The microorganisms employ different mechanisms in attaining multidrug resistance such as enzymatic deactivation of antibiotics, decreased cell wall permeability to antibiotics, altered target sites of antibiotic, efflux mechanisms to remove antibiotics, etc. Increasing resistance of S. aureus to last line of drug i.e., vancomycin, highlights the need for either development of new therapeutic agents or implementation of new strategies to control the resistance. Optimal use of existing antimicrobial agents, using alternative treatment options, reducing the used for antimicrobials by increasing immunity, application of nanoparticles in drug delivery, education of health professionals and patients, antibiotic policies and implementation of infection control measures.

Keywords: Methicillin, Vancomycin, Resistance, Nanoparticles.

1. INTRODUCTION

Staphylococcus aureus is a bacterium that belongs to the family of *Micrococcacea*. The bacteria are commensal organism mainly found in normal flora of the skin, intestine, upper respiratory tract and vagina (Lowy, 1998). *Staphylococcus aureus* can become pathogenic when physiological conditions such as pH, temperature and nutrient

availability are altered and become favourable for overgrowth (Mims et al. 2004). The Pathogenicity of *S. aureus* is determined by the production of toxins, such as the 33-kd protein-alpha toxin, exfoliatin A, exfoliatin B and Panton-Valentine leukocidin (PVL) toxins (Lowy, 1998). These toxins can be harmful to the host and cause various type of skin diseases like carbuncles, boils, folliculitis and impetigo and other complications, such as endocarditis, meningitis as well as toxic shock syndrome (TSS) (Mims et al. 2004). In 1878, Koch first noted that Gram-positive cocci responsible for different diseases depending on whether they formed pairs, chains or clusters. The *staphylococci* were identified as grape-like clusters of bacteria isolated from the pus of human abscesses (Ogeston, 1881). In 1884, Rosenbach differentiated species of *staphylococci* based on pigmentation. *Staphylococcus aureus* produced a golden yellow pigment are disease causing, whereas the non-disease causing strain was generally white (Rosenbach, 1884).

2. GLOBAL EPIDEMIOLOGY OF *STAPHYLOCOCCUS AUREUS*

In healthy individuals, the carrier rate of *S. aureus* range between 15% to 35% with a risk of 38% of individuals developing infection followed by a further 3% risk of infection when colonized with Methicillin susceptible *Staphylococcus aureus* (MSSA) (File, 2008) (Chakraborty et al. 2012). Some groups of individuals are more susceptible to *S. aureus* colonization than others including health-care workers, nursing home inhabitants, prison inmates, military recruits and children's (Ben-David et al. 2012) (Ho et al. 2008). In a study, conducted in 2007 by the University of the Witwatersrand and the University Hospital of Geneva, health-care workers are responsible for 93% of personnel to patient transmission of Methicillin resistant *S. aureus* (MRSA) (Albirich et al. 2008). Previously several outbreaks have been reported in Northern-Taiwan in 1997 that suggested MRSA transmission associated with health-care workers, including surgeons (Wang et al. 2001). Grundmann and colleagues reported a prevalence of > 50% in countries such as Singapore (1993-1997), Japan (1999-2000) and Colombia (2001-2002) while countries with a prevalence of 25% to 50% included South Africa (1993-1997), Brazil (2001), Australia (2003), Mexico and United States. The lowest prevalence of less than 1% was found in Norway, Sweden and Iceland (1993-1997) (Grundmann et al. 2007). In 2007, a prevalence of more than 50% of MRSA strains isolated from Cyprus, Egypt, Jordan and Malta was reported by Borg and colleagues. This high prevalence was due to overcrowding and poor hand hygiene facilities in the hospitals (Borg et al. 2007). From India, recently report 80% of MRSA strains were multidrug resistant. However all were uniformly sensitive to Vancomycin and Linezolic (Khan et al. 2007).

3. *STAPHYLOCOCCUS AUREUS* CARRIAGE AND DISEASE

Staphylococcus aureus is found as a commensal organism on the squamous epithelium of the anterior nares up to 20% of the population at any one time, however, it has been estimated that *S. aureus* can transiently colonize up to 60% of the human population (Foster, 2004). *S. aureus* can cause various types of infections ranging from minor skin abscesses to more serious invasive diseases. *S. aureus* commonly causes skin infection like boils, carbuncles, furuncles and impetigo, but after gaining access to the blood, it may be result in a major cause of endocarditis, osteomyelitis, pneumonia, toxic shock syndrome and septicaemia (Lowy, 1998). Many invasive staphylococcal infections are correlated with nasal carriage of infecting strains. Although immunocompromised patients may be at greater risk for developing an invasive *Staphylococcal* infection, healthy individuals may be also susceptible, especially if they are carriers (Peacock et al. 2001).

4. ANTIBIOTICS

Antibiotics are hailed as the greatest medicinal achievement of the 20th Century. Before their discovery, there was higher mortality rate due to microbial infection. The earlier development of vaccination had introduced immunity to some diseases and sterilization had helped to reduce the chance of infection from surgery. With the subsequent formation of germ theory and the work identify the role of specific bacteria in the diseases anthrax and tuberculosis, the search for a cure began (Kaufmann et al. 2005). In 1929, Fleming noted that the growths of bacteria could be inhibited by the presence of a mould, *Penicilium notatum*. This effect was caused by a metabolic product from the mould that was interacting with the staphylococcal culture (Fleming, 1929). Penicillin was the first of the family of β-lactam that now form the largest share of the antibacterial market.

4.1. Treatment and prevention of *S. aureus* infections

Penicillin is still the main drug of choice for *staphylococcal* infections as long as the isolate is sensitive to it (Kowalski et al. 2007). Cephalosporin, such as cefazolin or cephalothin can be administered as an alternative choice of treatment to the patient with delayed- type penicillin allergy. Semisynthetic penicillin, such as Methicillin, is used for patients with β-lactamase producing staphylococcal isolates. Patients who have an MRSA infection are treated with a glycopeptides known as vancomycin. Vancomycin is the empirical drug of choice for the treatment of MRSA (Michel et al. 1997). Patients who are intolerable to vancomycin are treated with a fluoroquinolone (ciprofloxacin); lincosamide

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(clindamycin); tetracycline (minocycline) or trimethoprim-sulfamethoxazole, which is also known as co-trimoxazole (Lowy, 1998).

Novel quinolones, such as ciprofloxacin with increased antistaphyloccal activity are available but their use may become limited due to the rapid development of resistance during therapy[1]. Several antimicrobial agents with activity against MRSA are currently evaluated and include: (i) oritavancin, a semisynthetic glycopeptide; (ii) tigecycline, a monocycline derivative (Guay, 2004) and (iii) DW286, a fluoroquinolone (Kim et al. 2003). Amongst these three antibiotics, tigecycline has been approved by the Food and Drug administration (FDA) in June 2005 (Stein et al. 2006).

Recently, an evaluation of glycosylated polyacrylate nanoparticles showed to have *in vitro* activities against Methicillin-resistant *Staphylococcus aureus* (Abeylath et al. 2007). Other recent investigative drugs include, silver nanoparticles, oleanolic acid extracted from *Salvia officinalis* (Sage leaves) (Yuan et al. 2008). Two novel antibiotics, neocitreamicins I and II, isolated from a fermentation broth of a *Nocardia* strain have shown to have *in vitro* activity against *S. aureus* and vancomycin-resistant *Enterococcus faecalis* (VRE) (Peoples et al. 2008). Accurate empirical therapy against *S. aureus* infections would be an important step towards the reduction of the development of resistance in the different strains.

4.2. Mechanism of action of Antibiotics

Antibiotics work in variety of ways. Some antimicrobial agents inhibit bacterial cell wall synthesis. These agents include β-lactam compounds such as penicillins (e.g. penicillin G, ampicillin and methicillin), cephalosporins and carbapenems, as well as monolactams and β-lactamase inhibitors. β-lactams inhibit the final stage of murein synthesis. This, by some undetermined mechanism, triggers murein hydrolases to lyse the cell. A related group of antibiotics that prevent a different step in cell wall synthesis are the glycopeptides, vancomycin and teicoplanin. Other agents have an antibacterial effect by inhibiting protein synthesis. Representatives of this group include the aminoglycosides, tetracyclines, macrolides and chloramphenicol which interfere with ribosome function. In addition, there are antibiotics that inhibit DNA synthesis, including quinolones, fluoroquinolones and sulfonamides (Normark et al. 2002).

5. MECHANISM OF ANTIBIOTICS RESISTANCE

Antimicrobial resistance is natural phenomenon & its effects, amplified by continuing and unnecessarily increase exposure to antimicrobials. Microorganisms have a distinct property to develop resistance against antimicrobials for their survival. They are enabling to carryout changes at genetic level & inherited these changes to next generation. They can also transfer these changes between same or different species thus contribute significantly in dissemination of resistance. In general mechanisms antimicrobial resistance come in four forms (www. tufts.edu).

- Enzymes that destroy or modify the antimicrobial substrate.
- Target site alteration like alteration of DNA gyrase, a target of fluoroquinolones.
- Bypass pathways that substitute for a metabolic pathway.
- Barrier to penetration or efflux pumps that exclude the agent.

5.1. Beta-Lactam Drugs

In Penicillins there are two main mechanism of resistance: (i) Cleavage of the β-lactam ring by β-lactamases/penicillinases, (ii) Alterations in the target PBPs that reduce their affinity to the penicillins. These two mechanisms are especially important to β-lactam resistance in *S. aureus*. Inactivation of β-lactam drugs: β-lactamase production appears to be the most common mechanism of resistance, with the discovery and identification of more than 100 distinct β-lactamases (Chambers et al. 1998). In terms of β-lactamase mediated resistance, the action of penicillin is prevented when the β-lactam ring of the antibiotic is hydrolyzed by β -lactamase. These molecules are extracellular enzymes which are divided into four types, A through D. In *S. aureus*, serotypes A and C have high activity. Genes for β-lactamase production, *blaZ oxpenP* are usually plasmid encoded, but these resistance genes may sometimes be found on the chromosome of the bacteria. *blaZ* is the gene that codes for the β -lactamase enzyme. In *S. aureus, blaZ* is carried by plasmids and is located on mobile genetic elements acquired from other bacteria. Three *S. aureus* transposons carry the *blaZ* gene: Tn4001, Tn4002 and Tn552. Tn552 encoded β-lactamase resistance is the most common in *S. aureus* plasmid.

Methicillin resistance is another important β-lactam drug resistance mechanism in *S. aureus.* Methicillin is a semi-synthetic penicillin derivative. Resistance to this β-lactam drug in *S. aureus* is of great concern to medical and scientific personnel. The genes for methicillin resistance are located on the chromosome. The genes in the signaling pathway for methicillin resistance are *mecA mecRl, mecR2* and *mecl. mecA* codes for a penicillin-binding protein, PBP2a (also called PBP2) which has a lower binding affinity for β-lactam drugs than regular PBPs. PBPs are transpeptidases involved in the construction of the bacterial cell wall. The regulation of methicillin resistance resembles that of β-lactamase expression. The chromosomally located gene, *mecRl,* like the plasmid located *blaRl,*

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codes for a sensor-transducer that is part of a two-component signalling system. *mecI* is a repressor of *mecA.* When *mecI* is bound to DNA, PBP2a is not produced. When *mecI* is unbound, then *mecA* is transcribed and PBP2a is produced. Lewis and Dyke found that *mecI* is also an effective regulator of *blaZ* and *blaI. mecR2*, like *blaR2*, is an accessory molecule involved in regulating PBP2a production (Lewis et al. 2000).

5.2. Aminoglycosides

The first method of resistance to aminoglycoside is via an alteration in the ribosomal target site. Mutations in the genes encoding ribosomal receptor proteins can result in changes in the structure of the ribosome such that it no longer binds the antibiotic or these receptor proteins may be absent. A second mechanism of resistance is impaired uptake of the antibiotic that diminishes the effective intracellular concentration of the antibiotic. It has been proposed that membrane impermeability may be a result of genotypic changes such as mutations in or deletions of porin proteins or other proteins involved in the transport and maintenance of the electrochemical gradient. Another suggested reason for impermeability is a phenotypic change owing to growth conditions under which the oxygen-dependent transport process is not functional (Chambers et al. 1998). The third mechanism of resistance is the most common and is due to the chemical inactivation of the amino glycoside by specific enzymes. Aminoglycosides may be acetylated at secondary amino groups by aminoglycoside acetyltransferases (AAC), adenylated at hydroxyl groups by aminoglycoside adenyltransferases (AAD) or phosphorylated at hydroxyl groups by phosphotransferases (APH). Modified aminoglycoside antibiotics no longer bind to ribosomes and accordingly are unable to inhibit proteins synthesis.

5.3. Tetracyclines

There are three main mechanisms of resistance to tetracyclines. 1) Decreased intracellular accumulation of the drug due to impaired influx or increased efflux via an active transport protein pump. 2) Ribosome protection due to the production of proteins which interfere with the tetracycline binding to the ribosome. 3) Enzymatic inactivation of tetracycline by chemical modification. In *S. aureus*, resistance is due to active efflux of the antibiotic out of the cell. Tetracycline resistance determinants may be chromosomally-encoded or plasmid-encoded (Lyon et al. 1987).

5.4. Glycopeptide

Vancomycin is most important member of this class which is last choice to treat *Staphylococcal* infection. There are two forms of vancomycin resistance have been demonstrated. The first form involves changes in the peptidoglycan synthesis (Walsh et al. 2002). There is a visible irregularly shaped & thickened cell wall, due to increased amount of peptidoglycan. There is decrease in cross linking of peptidoglycan strands resulting in the exposure of more D-Alanyl-D-Alanine residues (Hiramatsu et al. 1998). The second mechanism of resistance due to *vanA* operon, which is result of conjugation process between *E. faecalis* & MRSA strains. The *vanA* gene together with its regulator genes*, vanSR*, from vancomycin resistance *Enterococcus faecalis*(VRE) is carried by transposon, Tn1546 which is result into alteration of target site; the D-Ala-D-Lac instead of D-Ala-D-Ala (Gonzalez-Zorn et al. 2003).

5.5. Fluoroquinolone

This class include ciprofloxacin, ofloxacin, Norfloxacin, levofloxacin, grepafloxacin, trovafloxacin, etc and kill bacteria by inhibiting the DNA synthesis (Hooper, 2002). This class initially developed for the treatment of Gram-negative and Gram-positive bacteria other than *S. aureus*, thus exposure of S*. aureus* to fluroquinolone are minimal. *S.aureus* resistance to fluroquinolones is suggested to be as a result of exposure of the bacteria to fluroquinolone in mucosal and cutaneous surface of nasal cavity (Blumberg et al. 1991). Recently, a study reported an 85% fluroquinolone-resistance in MRSA strain (Udo et al. 2008). *S.aureus* develop resistance against fluoroquinolones by altering the target site i.e. DNA gyrase and topoisomerase, which are responsible for DNA replication.

6. DIAGNOSTIC IDENTIFICATION

The *S.aureus* identification is based on the phenotypic & genotypic investigation (Fluit et al. 2001). Phenotypic identification of *S.aureus* include Gram-staining, Catalase, Coagulase, DNAse, culture on Mannitol salt agar or blood agar & sugar fermentation test (Waldvogel, 2000). Upon identifying *S.aureus* by Gram staining(Gram positive cocci), Catalase(positive), fermentation test (oxidase positive) & tube coagulase(positive) or DNAse test (positive), the sample is grown on Mannitol salt agar or blood agar at 37^{O}C for 18 to24h . The colonies appear yellow on MSA & creamy white on blood agar. *S.aureus* colonies are subjected to antimicrobial susceptibility testing by Kirby Bauer disk diffusion method, automated methods such as the Vitek (bioMerieux, France) & Microscan (Dade Microscan, West Sacramento, CA) systems or conventially available method including Latex agglutination assay kits (Brown et al. 2005). Various molecular techniques have been implemented for the rapid identification of MRSA and VRSA strains is based

on the amplification of *mecA* & *vanA* gene respectively, which confer resistance to Methicillin & vancomycin (Mcclure et al. 2006).

7. CONCLUDING REMARK

The evolving of resistance in *Staphylococcus aureus* is continue to currently available antimicrobial drugs by changing in their genetic information by various mechanism. *Staphylococcus aureus* was developed resistance to almost all class of antibiotics. Vancomycin from glycopeptides category is last resort of drug. Hence there is need of implementation of new strategy and policies to controlled antibiotic resistance problem so that we may not fall back into pre-antibiotic era. The most effective way to prevent emergence of antibiotic resistance is by continuous surveillance of antibiotic resistance profile, reduce misused of antimicrobial drug by proper diagnostic procedure, development of significant new antimicrobial agents and also need of effective education & training to the public about the limitation of antibiotics so that they can utilized it carefully & also the need to adopt a personal hygiene.

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